

RELATIONSHIPS BETWEEN THE OUTCOME OF *PLASMODIUM FALCIPARUM* INFECTION AND THE INTENSITY OF TRANSMISSION IN AFRICA

T. SMITH, G. KILLEEN, C. LENGELER, AND M. TANNER
Swiss Tropical Institute, Basel, Switzerland

Abstract. Establishing the relationship between transmission intensity and health outcomes is crucial for the planning of long-term malaria control programs. Unfortunately this is fraught with methodologic difficulties. In this report, we address some of these problems by considering some important parameters that have previously been ignored. One important consideration is that the incidence of infection for *Plasmodium falciparum* malaria is much lower than entomologic inoculation rates (EIRs), especially at higher transmission levels. Moreover, biting rates of malaria vectors per host depend on his or her biomass and thus age. We propose an algorithm for estimating human infection rates from the EIR with allowance for these two factors. We then re-analyzed 1) data on EIR and age-specific incidence of clinical malaria in two villages in Senegal and 2) a survey of infant and child mortality rates across Africa. In each case, we review analyses of incidence in relation to the EIR and carry out a new analysis of morbidity and mortality rates in relation to the estimated incidence of infection (h). Reduction in malaria transmission may result in a shift of acute malaria attacks to older ages, and thus have little impact on life-time risk of clinical attacks. However, our analysis of the Senegalese data indicates that the peak incidence rate of disease relative to infection rates is in the youngest age groups in both the villages of Dielmo (EIR = 200 infectious bites per year) and Ndiop (EIR = 20). This suggests that simple models of acquired clinical immunity can explain age-incidence profiles better when incidence is expressed in relation to h , than when expressed in relation to the EIR. Relationships of malaria transmission intensity (in endemic areas) with overall mortality are very different from those with acute morbidity. Infant mortality rates (IMRs) decrease substantially when the EIR is reduced, probably largely because of prevention of indirect mortality. However, we were not yet able to draw strong conclusions about the shape of relationships between the IMR and h because many of the available data points have similar values of h . The effects of transmission reduction on mortality rates in older age groups are also uncertain. However, it is clear that reduction of exposure during infancy is not reflected in increased mortality at older ages.

INTRODUCTION

The bite of an Anopheline mosquito with malaria sporozoites in its salivary glands can have health consequences ranging from minimal discomfort to death due to an acute attack of *Plasmodium falciparum* malaria. The outcome of any given bite is uncertain and depends, among other things, on the immune status of the host. Reductions in malaria transmission may slow down the acquisition of this immunity, and a sound understanding of these relationships is crucial for the long-term planning of control efforts. However, there is surprisingly little firm evidence on the epidemiologic consequences of delaying exposure and this remains a subject of active investigation.

The entomologic inoculation rate (EIR), defined as the number of infective mosquitoes biting each human host in a unit time interval, is a key measurement of the exposure of human populations to malaria. A number of studies have considered how clinical outcomes relate to the EIR, since this determines the public health impact of any intervention that works by reducing malaria transmission. In this report, we focus on two such studies, an intensive study of clinical malaria in Senegal¹ and a literature survey on the relationship between mortality in infants and children less than five years old and EIR.² We do not investigate here the relationship between transmission intensity and severe malaria disease because of potential confounding by factors such as access to treatment.

In inter-age and inter-population comparisons, the EIR can be a poor indicator of parasitologic challenge for two reasons. First, the standard method for determining the EIR is to use human landing catches of mosquitoes made by adult male mosquito collectors. Since the biting rate of malaria vectors per host depends on his or her biomass^{3–5} (Figure 1), this

overestimates the challenge faced by small children. Second, since the probability that an inoculation is effective (the success probability) decreases as the EIR increases, the infection rate is not proportional to the EIR⁶ (Figure 2). There is a similar relationship between *P. falciparum* prevalence and EIR when different study sites are compared⁷ and relationships similar to those in Figure 2 have also been found in a study of infection incidence in infants in Tanzania⁸ who have little prior exposure to malaria. This attenuation phenomenon therefore probably represents an effect of innate, not acquired, immunity.

These attenuating steps complicate the interpretation of analyses of exposure-response relationships. We have now used the data of Port and others⁵ and Beier and others⁶ to develop an algorithm to convert EIR measurements to estimates of the daily incidence of infection. We use this to estimate the incidence of infection corresponding to the EIR measurements recorded in the two studies on which we focus. We then discuss the implications of the relationships between these two major health outcomes and EIR, and also how these differ from the relationships with estimates of incidence of infection.

METHODS

Estimation of the incidence of infection from the EIR. *Differential feeding by mosquitoes depending on body weight.* Port and others⁵ reported a series of experiments in The Gambia in which fed mosquitoes were collected from the mosquito nets of 35 groups of people who normally slept together. The blood meals were assigned to hosts using hapto-globin or ABO typing, and the proportion of mosquitoes that had fed on each host was analyzed in relation to the host's contribution to the total biomass and surface area of

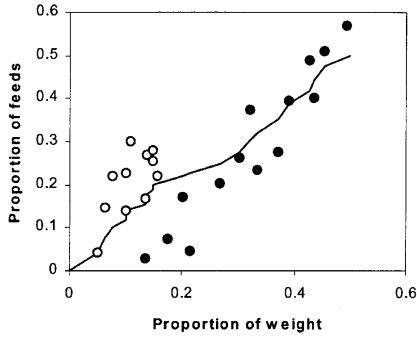


FIGURE 1. Proportion of *Anopheles gambiae* s.s. feeding on a host in relation to the proportion of total weight of the hosts under the same mosquito net. Data for each host are those that composed <50% of the total weight of those sleeping under the same mosquito net. Redrawn from the data in the original publication by Port and others.⁵ ○ = children less than 18 months of age; ● = older individuals. — = fitted curve (see Methods).

the people sleeping in the mosquito net (Figure 1). Similar relationships were found between the biting rate and both weight and the surface area of the host, and the investigators could not determine which of these was the key determinant of how many mosquitoes bite an exposed host. For simplicity, we have considered only host weight in our analyses. The original paper also reported similar relationships between host size and biting rate whether all mosquitoes were considered or only *An. gambiae* s.s. We have based our analyses only on the data for *An. gambiae* s.s.

Let w_i be the proportion of the total weight of people sleeping under the net contributed by person i . The expected proportion of mosquitoes feeding on that person, $f(w_i)$, (equivalent to the feeding likelihood⁹) is then a function of w_i satisfying the constraints $w_i = 0 \Leftrightarrow f(w_i) = 0$ and $w_i < w_j \Leftrightarrow f(w_i) < f(w_j)$. These constraints are implied by the fact that there is

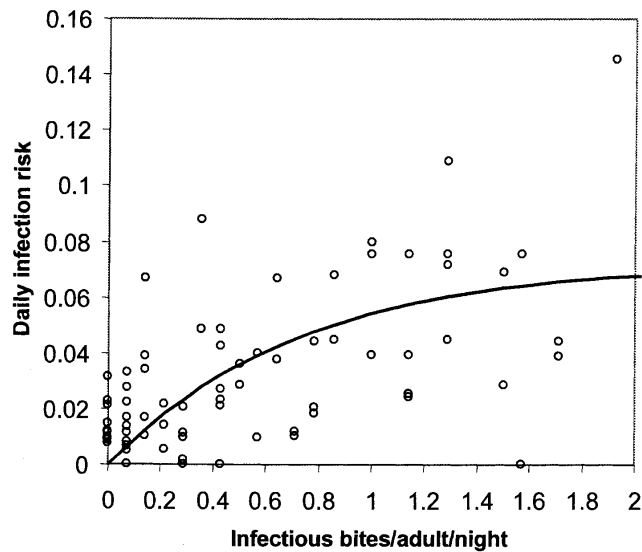


FIGURE 2. Infection rate in relation to the entomologic inoculation rate ○ = daily infection probability, h , estimated for each cohort and the two-week period from $h = 1 - (1 - p)^{1/14}$, where p is the proportion of children at risk who became infected during the 14-day interval. — = fitted curve (Equation 3). Data are those of Beier and others.⁶

no threshold weight, below which the host will not be bitten, however both the weight and biting rate must be positive, and the estimated biting rate should increase with the biomass of the host (Figure 1). Moreover, two hosts of equivalent weight sleeping together are equally likely to be bitten so that $w_i = 0.5 \Leftrightarrow f(w_i) = 0.5$.

To obtain estimates of $f(w_i)$ as a function of w_i we fitted a Bayesian monotone regression model to the original published data. This allowed the fitted relationship to be as flexible as possible within the constraints listed above (Appendix 1).

The ratio between the number of bites received by individual i and its companion(s) is $f(w_i)/[1 - f(w_i)]$. This quantity corresponds to the expected ratio between the inoculation rates of any individuals whose relative weights are $w_i : 1 - w_i$. We used this relationship to convert the values of $f(w_i)$ to relative EIR values for different ages by computing the mean growth in weight for a typical African rural population (from Tanzania).¹⁰ Defining W_a as the mean weight in age group a , we estimated E_a , the adjusted EIR, for age-group a from

$$E_a = E_{20-25} \frac{f\left(\frac{W_a}{W_a + W_{20-25}}\right)}{1 - f\left(\frac{W_a}{W_a + W_{20-25}}\right)}, \quad (1)$$

where the age group 20–<25 years, a typical age for mosquito collectors, is used as a standard for both weight and EIR.

Dependence of force of infection on EIR. Beier and others⁶ studied the reinfection of 21 cohorts of between 43 and 50 children six months to less than six years old, each followed up during four successive two-week periods, following initial clearance of *P. falciparum* parasites (Figure 2). They reported entomologically assessed exposures in terms of the numbers of sporozoite-positive mosquitoes biting during each 14-day period.

We used the program WinBUGS version 1.3 (Medical Research Council Biostatistics Unit, Cambridge, United Kingdom) to fit a parametric relationship between the probability of infection, in children aged 0.5–6 years in a given day, $h_{0.5-6}$, and EIR of the form

$$h_{0.5-6} = g [1 - \exp(-\beta E_{20-25})], \quad (2)$$

where g and β are both parameters describing the host susceptibility. We allow for imprecision in the EIR assessment by assuming Poisson variation in the counts of sporozoite positive mosquitoes.

To predict h_a , the incidence of infection in age group a , from a given measured EIR (E_{20-25}), we use Equation 1 to estimate E_a and $E_{0.5-6}$ and then substituted the relative number of inoculations into Equation 2, i.e.,

$$h_a = g \left[1 - \exp\left(-\beta \frac{E_{20-25} E_a}{E_{0.5-6}}\right) \right] \quad (3)$$

Studies of outcomes in relation to incidence of infection. To examine effects of age of the host and malaria transmission intensity on the incidence of clinical malaria, we reanalyzed data from Ndiop (EIR = 20) and Dielmo (EIR = 200) in

Senegal¹ (Figure 3). We made estimates of the age-specific incidence of infection, h_a , for each site and month of the year separately, using the published seasonal patterns of transmission^{1,11} as the source for monthly EIR figures. We then compared the age-incidence patterns reported in the original publication with estimates of the ratio of incidence of clinical malaria to h_a , i.e., of the number of clinical episodes for each new infection event.

To evaluate effects of transmission intensity on infant mortality we have re-examined a summary how published African infant mortality rates (derived from prospective demographic surveillance) are related to EIR (Figure 4a)², calculating for each published EIR estimate a corresponding value of h_a . The

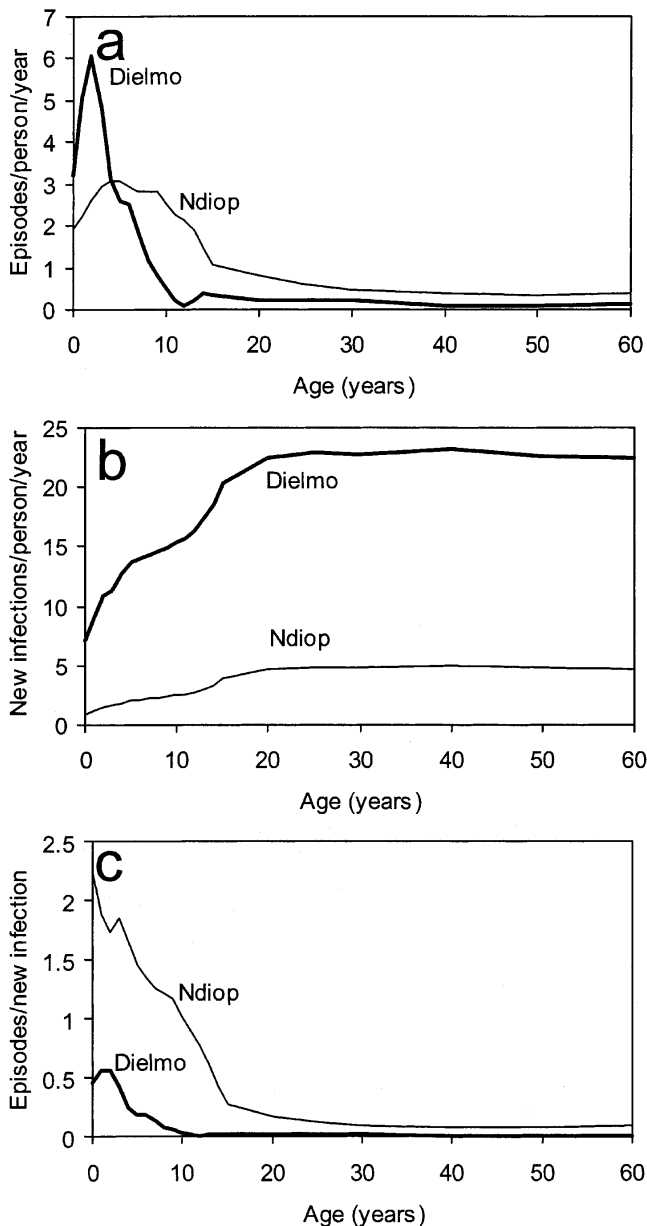


FIGURE 3. Incidence of clinical malaria in Dielmo and Ndiop, Senegal. **a**, Age-specific incidence of clinical episodes, redrawn from the original publication by Trape and Rogier.¹ **b**, Estimated incidence of new infections (h_a) by age. **c**, Ratio of clinical episodes to incidence of new infections (h_a) by age.

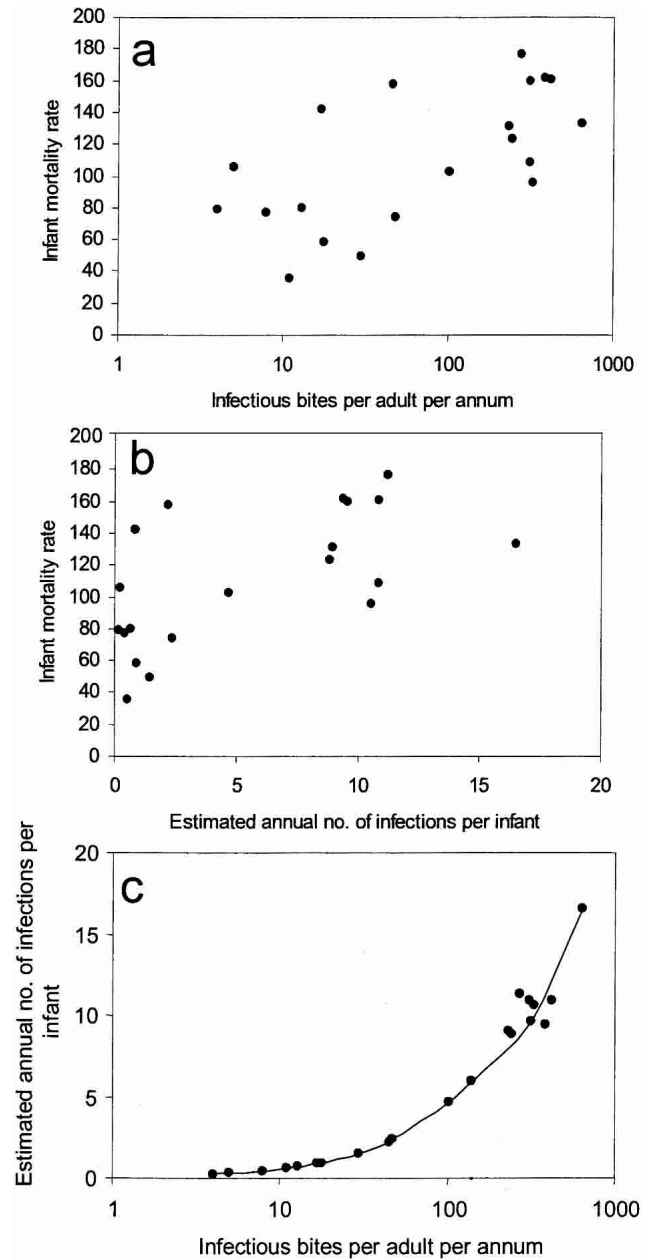


FIGURE 4. Infant mortality rate in relation to the entomologic inoculation rate (EIR) at 20 sites in Africa. **a**, Infant mortality rates by (unadjusted) EIR, redrawn from the original publication by Smith and others.² **b**, Relationship of infant mortality rate to incidence of infection (h_a). **c**, Estimated incidence of infection (h_a).

extent to which entomologic inoculations are clustered in time affects estimates of the corresponding infection rates. To allow for this we used a climate-based suitability model¹² to obtain estimates of the length of the transmission season at each site. This model classifies each month of the year for all locations in Africa as either suitable or unsuitable, based on rainfall and temperature data. For purposes of estimating the effects of seasonality on the success rate of inoculations, we assumed that the entomologic inoculations were uniformly distributed throughout the transmission season defined by the seasonality model, and then applied Equation 3 to the monthly inoculation rates.

RESULTS

Methodology for estimating h_a . Our reanalysis of the data of Port and others⁵ provided us with a continuous fitted curve allowing us to estimate the rate at which human hosts are bitten by *Anopheles*, as a function of body weight (Figure 1). The curve agrees with the original analyses, which concluded that the smallest children are bitten more frequently than would be predicted by a model of proportionality. Whereas Port and others⁵ fitted separate straight lines for children less than 18 months old and older individuals, the curve we have fitted serves our purpose better because it provides a continuous function with which to estimate the relative biting rate for any age of host.

The relationship that we estimated between the infection incidence in children, $h_{0.5-6}$ and the EIR values for the same cohorts in Kenya (E_{20-25}) shows a good fit to the data (Figure 2) with estimates of $g = 0.073$ (SE = 0.011) and $\beta = 0.097$ (SE = 0.025) (with time units of one day). This curve is similar to that reported in a study of infants in Tanzania,⁸ but with rather higher estimates of incidence of infection.

Analysis of clinical malaria incidence in Senegal. The raw age-specific incidence data from Dielmo (Figure 3a) show the typical age-incidence pattern for malaria in very high transmission areas with the peak of malaria incidence in very young children, and with very few clinical episodes attributable to malaria in older children and adults. Ndiop shows the typical pattern for a lower-transmission area, with the peak of incidence in older age groups.

The values of h_a estimated for Dielmo and Ndiop from Equation 4 illustrate the age-dependence that we estimate (Figure 3b). The steep increase with age in h_a because of increasing body mass results in very different age profiles of the estimated number of episodes per new infection (Figure 3c), from those in Figure 3a. In both villages, the peak incidence of disease relative to that of infection is in younger children, one year of age in the case of Dielmo, and less than one year of age in Ndiop. However the number of episodes of disease in those less than one year of age in Ndiop is even higher than the infection rate.

The lower success rate of inoculations at high EIR than at low EIR (attenuation) also has substantial effects. In adults, the estimated infection rate in Ndiop is about one-fourth of that for Dielmo, despite the 10-fold difference in EIR.

Analysis of mortality data. The infant mortality rate (IMR) shows a strong and statistically significant positive relationship with EIR^2 (Figure 4a). The reported EIR values span more than three orders of magnitude (thus, we plotted them on a logarithmic scale) and the curve fitted in the original publication² parameterizes the IMR as a function of the logarithm of the EIR, i.e.:

$$IMR_0 = IMR_1 [\ln(E)]^{0.127}, \quad (4)$$

where IMR_1 is equal to the IMR at an EIR of one infectious bite per year (approximately equal to the lowest level of endemic transmission), which is estimated to average 62 per 1,000 for the given study sites. However, there is considerable scatter between the points, making it very uncertain what shape of curve, if any, should be fitted.

The estimated duration of the transmission season for the 20 localities studied ranged from 4 to 12 months (mean = 6.8

months, SD = 2.0). At low EIR values, Equation 3 is equivalent to

$$h_0 \approx g\beta \frac{E_{20-25}E_0}{E_{0.5-6}}, \quad (5)$$

i.e., h is roughly proportional to the EIR. The seasonal distribution of the inoculations then makes little difference to h_0 because the same constant of proportionality, $g\beta E_{20-25}/E_{0.5-6}$, applies to the data for each month. However, when there are a large number of inoculations in a single month, h_0 for that month tends towards the upper limit, g , implied in Equation 4. This has the consequence that at high EIR levels, the extent of attenuation depends crucially on the duration of the transmission season, with the success probability of an inoculation higher when the bites are distributed more evenly over the year. In the particular dataset available, several of the high EIR study sites have a transmission season that is short but intense, so that the estimated value of h_0 for each month of transmission is close to g . This has the effect of bringing the annualized estimates of the incidence of new infections (h_a) closer together at high EIR than they would be if they fell on a smooth curve drawn through the average value of h_a at each EIR (Figure 4c), and the ranking of the values of h_a for these points differs from the ranking of the EIR.

This means that, if anything, it is even more difficult to discern any pattern in the IMR/h_0 relationship at high values of h_0 (Figure 4b) than it is to discern pattern in the IMR/EIR relationship (Figure 4a). The mortality rates for children 12–59 months of age in the same studies were all much lower than mortality rates in infancy and there were no obvious relationships between these mortality rates and either EIR^2 or h_a .

DISCUSSION

We have explored the extent to which two well established, but often forgotten phenomena affect the relationship between malaria transmission and health outcomes. These are age-dependence in exposure to mosquito bites, and the saturation of the incidence of infection as EIR increases.

Our attempt to make age-specific estimates of h from published EIR data is of necessity crude. It is not obvious that we have chosen the best measure of host body size, nor that the same calibration of biting rates by body size should be used for all transmission settings and sleeping patterns. Similarly, we make a strong assumption by applying Equation 3 for all age groups with the same parameters g and β .

The very high ratio of clinical attacks to estimated new infections in the youngest age group in Ndiop also suggests that our model does not account for all the factors leading to age-dependence in infection incidence. Since all these clinical attacks were treated, repeated episodes of disease caused by the same infections cannot explain the high clinical attack rate, so we infer that the success rate of inoculations in infants is actually higher than our algorithm suggests. One possible explanation for this would be that pre-erythrocytic immunity (which is not allowed for in our calculations) also plays a role in determining the age-dependence of h . This would predict that the h increases less with age than we have estimated.

Our estimates of h_a cannot therefore be considered definitive, but they nevertheless contribute to our understanding of epidemiologic patterns by clarifying which relationships can, and which cannot, be accounted for by effects of host biomass and of saturation of h_a at high EIR.

There is strong evidence both from molecular typing¹³ and from patterns of seasonality in morbidity¹⁴ that clinical malaria is normally caused by newly invading parasites, and the most severe symptoms generally accompanying the first peak of parasite density after infection. It follows that in the short-term, any reduction in EIR will decrease the incidence of clinical episodes in proportion to the effect on the force of infection.

Reductions in transmission intensity, however, also reduce immunologic stimulation, and this may have longer-term effects, in particular resulting in shifts of the peak in the age-incidence profiles to older ages, as seen in the comparison of Dielmo and Ndiop. Consequently, it appears that a reduction in EIR will have little effect on the total number of episodes in a lifetime. However, without a reliable model for clinical immunity, the long-term effects of any intervention cannot be predicted with confidence. One model is that *P. falciparum* consists of a number of distinct strains, and that clinical episodes result only on the first occasion that a strain infects a host.¹⁵ Within this model, each infection confers long-term clinical immunity so that subsequent infections with the same strain do not result in clinical attacks. However, analysis of exposure-incidence relationships in Tanzanian infants suggested that the main determinant of clinical immunity is the duration of exposure to blood-stage parasites, and not the number of inoculations *per se*.¹⁶ There is also evidence for a role of short-term effects that depend on cross-protection between co-infecting parasites.^{17,18}

None of these models alone can explain why the peak incidence is not in the youngest children. An explanation for this is provided by Figure 3c, which indicates that small size is likely to be the main explanation for why incidence of clinical episodes is lower in infants. The surprisingly low incidence in infants in Dielmo could be due to passive immunity during the first 3–6 months of life, which means that infections then only rarely result in clinical episodes.¹⁹ In contrast, our analysis suggests that in the youngest children in Ndiop effectively all new infections result in clinical malaria attacks. Indeed, when considered relative to the infection rate, the surprise is the very high incidence in infants in Ndiop and low incidence in Dielmo. Part of the explanation could be due to the lack of allowance for acquired immunity against pre-erythrocytic stages of the parasite (see above), meaning that incidence of infection in infants in Ndiop may actually be higher than we have estimated.

While it is of some concern that reducing malaria transmission in endemic areas does not necessarily substantially reduce the incidence of clinical episodes, the public health impact of malaria depends mainly on its effects on mortality. The impact on mortality appears to show very different relationships with transmission intensity from those on acute morbidity.

The relationships of malaria-specific child mortality rates with EIR are unclear.^{20,21} Part of the explanation for this is that verbal autopsies for malaria are known to perform poorly,^{22–25} leading to very imprecise estimates of malaria-specific mortality. Because malaria can be effectively treated

the case-fatality rate also varies enormously depending on the effectiveness of the health services. It can be especially high in epidemics, when a high incidence rate during a short period results in social disruption.

The analysis of malaria-specific mortality is further complicated by the abundant evidence that malaria causes many deaths indirectly that are classified as due to other causes, but that would have been avoided in the absence of malaria.^{26,27} Much of this indirect morbidity and mortality is accounted for by acute respiratory infections, and co-infection with other pathogens worsens the outcome in malaria,²⁸ so many deaths are clearly multi-factorial. Clear evidence for this came from the decreases in all-cause mortality in malaria control trials in the 1950s to the 1970s, which were greater than could be explained from the malaria rates.^{27,29} A particularly telling example is the convergence of death rates in malarious districts of Sri Lanka with those in districts without malaria, when effective control was introduced. The decreases in mortality were much greater than the mortality rates that had previously been attributed to malaria.²⁷ A second good example is the disappearance of epidemics of acute respiratory infections from sugar plantations in coastal Guyana when the malaria was eradicated.³⁰ Prior to eradication, these epidemics were synchronized with those of malaria.

Ultimately, it matters little whether the primary cause of a death is malaria, so for most purposes it is more relevant to analyze all-cause mortality than to concentrate only on diagnosed malaria. Randomized controlled trials of insecticide-treated bed nets and curtains have demonstrated efficacy of 14–42% in reducing all-cause mortality in children one month to five years old^{31–36} across a range of transmission intensities. This is overwhelming evidence for a benefit of transmission reduction. The strong increase in IMR with EIR (Figure 4a) reinforces this conclusion and confirms the substantial public health benefit in reducing malaria transmission. However, the number of data points relating IMR to EIR is limited, and there is uncertainty about what shape of curve, if any, should be fitted through them to predict the effects of any specific reduction in transmission.³⁷ This motivated us to compute h_0 , since we hoped to test whether the saturation effect suggested by Figure 4a can be accounted for by the saturation in the relationship between h_0 and the EIR (Figure 2). Since h_0 itself tends to a limit as the EIR increases, it would be surprising if mortality, a secondary consequence of infection, failed to plateau at high EIR, but it is less obvious what relationship might be anticipated between IMR and h_0 (Figure 4c). In fact, by demonstrating that the available points covered only a limited range of values of h_0 , our analysis served less to clarify this relationship than to emphasize the inadequacy of the available data for estimating it. There is clearly a need for further investigations of these relationships, and measurements of malaria transmission intensity currently in progress at a number of demographic surveillance sites across Africa will have an important role in extending the dataset.

For children 12–59 months old, the limited data currently available do not suggest any particular relationship between the mortality rates and either EIR² or h_a . In the trials of insecticide-treated bed nets, the benefits of transmission reduction were also clearest in the youngest children, and at high levels of transmission (in Ghana) the benefit was limited to children less than two years of age at the start of the trial.³⁸

Unlike the effects of transmission reduction on clinical episodes, long-term follow-up of two of these trials after the control group was given the intervention indicated that the increased survival in very young children has no price in higher mortality later on³⁸ (Diallo DA, unpublished data). This is in keeping with findings from trials of indoor residual spraying.^{29,39}

The finding that the main benefit of reducing transmission on mortality is in the youngest children is also at variance with effects on clinical episodes, since the latter are infrequent in the first few months of life. It is likely that the effects on infants largely relate to indirect mortality. Life-threatening acute respiratory infections and diarrhea and thus co-infection are most frequent in infants, and the mortality risk from severe anemia is highest in the second half of the first year of life. Sick infants have the greatest difficulty communicating their distress to care givers. Perhaps most importantly, low birth weight caused by malaria in pregnancy probably leads to a very substantial component of infant mortality.⁴⁰ In endemic areas, malaria prophylaxis during pregnancy is estimated to correspond to lead to an average increase of 0.101 kg in the birth weight of first-born children, corresponding to a reduction of 11 per 1,000 in their neonatal mortality rate.⁴¹ Unfortunately no studies have examined the relationship between either birth weight or placental malaria and the EIR, so it is not possible to dissect out how these specific risk factors are affected by incomplete malaria control.

These indirect effects may well be most important in determining the burden of malaria in Africa and it is here that very substantial benefits are likely to be seen when levels of transmission are reduced.

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Authors' address: T. Smith, G. Killeen, C. Lengeler, and M. Tanner, Swiss Tropical Institute, Socinstrasse 57, PO Box CH-4002, Basel, Switzerland, Telephone: 41-61-284-8273, Fax: 41-61-271-7951, E-mail: Thomas-A.Smith@unibas.ch.

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APPENDIX 1

To estimate $f(w_i)$, we fitted a Bayesian monotone regression model to the data for all those persons who contributed less than 50% of the weight of people sleeping under their respective mosquito nets. Let r_i be the number of mosquitoes feeding on person i , where i indexes the persons in rank order of w_i , and let n_i be the total number of mosquitoes feeding under the corresponding net. For each value of w_i , we assumed a binomial likelihood, i.e., $r_i \sim \text{Bin}[n_i, f(w_i)]$.

To ensure that $f(w_i)$ was an increasing function of w_i , we calculated it from $f(w_i) = f(w_{i-1}) + \delta_i$ where $f(w_0) = 0$ and the δ_i are estimated using a Markov Chain Monte Carlo algorithm using the program WinBUGS 1.3.⁴² The δ_i values were constrained to be positive by assigning Uniform (0, 1) prior distributions to a set of parameters δ'_i and computing δ_i from $\delta_i = \frac{0.5\delta'_i}{\sum_j \delta'_j}$. This transformation also constrained $f(w_i)$ to be

< 0.5 for the people included in the analysis.